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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,728	05/24/2001	Sandra J. Rosenthal	11672N/020878	2786

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STITES & HARBISON PLLC
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NASHVILLE, TN 37219-2376

EXAMINER

CEPERLEY, MARY

ART UNIT	PAPER NUMBER
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1641

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DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n N .

09/864,728

Applicant(s)

ROSENTHALL ET AL.

Examiner

Mary (Molly) E. Ceperley

Art Unit

1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 and 17-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2-4 . 6) ☐ Other:

Art Unit: 1641

1) In order for the Jacoby reference cited in the September 10, 2001 Information Disclosure statement to be published on the front of any patent issuing from this application, applicants must provide appropriate bibliographic data including journal/book name, volume and page numbers, and publication date.

2) Applicants' election without traverse of Group II, claims 8-16 in Paper No. 5 as further defined by the species shown at page 2 of the February 24, 2003 response (Paper No. 8) is acknowledged. Claims 1-7 and 17-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Claims 8-16 are examined on the merits in this Office action to the extent that they encompass the elected invention. Claims 8-16 should be amended to be limited to the elected invention. The compounds depicted in the first structure of page 38 and the first and second structures of page 40 have been included in the examination on the merits since these compounds are considered to be patentably indistinct from the elected invention.

3) Although specific claims are cited in the rejections below, these rejections are also applicable to all other claims in which the noted problems/language occur.

4) The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5) The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1641

6) Claims 8 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as being based on a specification which does not contain an adequate enabling written description of "X" defined as "an organic compound capable of bonding to a detectable substance". Support for this term appears at page 23, line 20 through page 24, line 14 of the specification wherein it is stated that "the organic part of the nanocrystal compounds...are biologically active compounds" which "will bind to detectable substances". However, it is unclear from the description what each of the "detectable substances" and "biologically active compounds" is. Is the "biologically active compound" a hapten (drug), for example, and the "detectable substance" the corresponding antibody, or is the "biologically active compound" the antibody receptor and the "detectable substance" a hapten? The discussion of "an affinity molecule...in combination with a dye molecule" at page 24, lines 3-6 of the specification fails to clarify the difference between the "biologically active compound" and the "detectable substance". How is the "affinity molecule...in combination with a dye molecule" related to either the "detectable substance" or the "biologically active compound"?

7) Claims 8-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of coated nanocrystal compounds as described at pages 25 *et seq*, does not reasonably provide enablement for the preparation and use of nanocrystal compounds wherein an -S- moiety present on the nanocrystal *per se*, as claimed, is directly substituted with a PEG linker-drug moiety. The description of page 25 of the specification is limited to the preparation of trioctylphosphineoxide coated nanocrystals linked to a drug (see also, pages 99-101). The specification provides no support for the preparation of nanocrystal-S-PEG conjugates of the instant claims, specifically the nanocrystal-S- linkage. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Art Unit: 1641

8) Claim 11 is rejected under 35 USC 112, first paragraph, as being based on a specification which does not contain an enabling written description of how to make and use the compounds of formulas (II), (V), (VII), and (X) wherein the point of attachment of the linker is at other than the 2-position of the benzene ring. It is further not clear that the nanocrystal-drug conjugates wherein the point of attachment of the linker is at other than the 2-position of the benzene ring would have the requisite utility of binding to the corresponding drug receptors.

9) Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) In claim 8, it is unclear what is meant by the term "an organic compound capable of bonding to a detectable substance". See the discussion in paragraph **6)** above.

b) In claim 8, the non-terminal group "R" is improperly defined as a terminal moiety "SH".

c) Claim 10 is inconsistent with independent claim 8. Claim 10 inconsistently states that "R represents the attachment point to the nanocrystal compound" i.e. no linker would be present.

O/C Further the term "nanocrystal compound" (incorrectly used in claim 10) includes both the "organic compound" and the "nanocrystal".

d) It is unclear how the thioether group (-S-) is attached to the "nanocrystal" i.e. it is unclear what moiety on the "nanocrystal" is used to conjugate the thiol-terminated linker to the "nanocrystal".

10) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

Art Unit: 1641

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11) Claims 8-10 and 12-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25-33 and 37 of copending Application No. 09/864,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of instant claim 8 wherein $R = SH$, $Z = CH_2$ and $R_2 = CO$ overlap with the compound of claim 25 (new numbering) of 09/864,731 wherein $R_2 = CO$ and $R_3 = SH$.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2
M **12)** Claims 8-16 are rejected under judicially created doctrine as being drawn to an improper Markush group. The members of the Markush group do not contain a substantial structural feature in common which is disclosed as being essential to the stated utility. The single common core structure of the compounds encompassed by formula (I) of claim 8 is a nanocrystal, a structure admittedly well known in the art as a fluorescent label. Both the linkers and the "organic compounds" encompassed by formula (I) are so diverse in nature that a reference which would anticipate or render obvious one linker/"organic compound" combination would not necessarily suggest or render obvious another linker/"organic compound" combination.

13) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

Art Unit: 1641

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14) Claims 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Bruchez et al (U.S. 6,274,323) or Bawendi et al (U.S. 6,306,610):

Each of the references describes nanocrystal-PEG-ligand conjugates which are useful in analytical methods for detecting biological molecules. These are the same conjugates which are described in instant claim 8 with the exception that the specific serotonin/melatonin drug ligands of the elected invention are not specifically described by the references. See Bruchez et al: col. 9, lines 11-18; col. 11, line 62 – col. 12, line 5; col. 18, lines 6-58; col. 21, lines 23-43; col. 21, line 59 – col. 22, line 21 (especially col. 22, lines 13-14); Bawendi et al: claims 1, 4, 5, 8, and 16; col. 19, line 22 – col. 20, line 11.

Serotonin and melatonin are both admittedly well known drugs. See page 9, line 12 – page 10 of the instant specification.

In view of the fact that both Bruchez et al and Bawendi et al both indicate that a wide variety of ligands are useful as moieties in their disclosed nanocrystal-PEG-ligand conjugates, it would be obvious to substitute one well known ligand for another, i.e. the well known ligands melatonin or serotonin, in either the Bruchez et al or Bawendi et al conjugates, as claimed, with the expectation of obtaining a similar useful analytical reagent for the determination of the corresponding specific binding pair member (i.e. antibodies specific for serotonin or melatonin).

15) Claims 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over **a)** each of Bruchez et al (U.S. 6,274,323) or Bawendi et al (U.S. 6,306,610) taken in combination with each of **b)** Zalipsky (Bioconjugate Chem. (1995), 6, 150-165) or Zalipsky et al (Eur. Polym. J. (1983), 12, 1177-1183).

Each of references **a)** is applied for the reason stated in paragraph **14)** above.

Art Unit: 1641

Zalipsky and Zalipsky et al each describe the attachment of PEG to biologically active molecules, including drugs, through a variety of terminal functional groups present on the PEG moiety. See both articles in their entirety.

In view of the fact that both Bruchez et al and Bawendi et al both indicate that a wide variety of ligands are useful as moieties in their disclosed nanocrystal-PEG-ligand conjugates, it would be obvious to substitute one well known ligand for another, i.e. the well known ligands melatonin or serotonin, in either the Bruchez et al or Bawendi et al conjugates, as claimed, with the expectation of obtaining a similar useful analytical reagent for the determination of the corresponding specific binding pair member (i.e. antibodies specific for serotonin or melatonin). The use of specific terminal functional groups on the PEG linking moiety of references **a)** constitutes an obvious, routine choice among the equivalent functional groups described by Zalipsky and Zalipsky et al which have not been described as critical to the practice of the invention.

16) Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. (Molly) Ceperley whose telephone number is (703) 308-4239. The examiner can normally be reached from 8 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached at (703) 305-3399. The fax phone number for responses to be filed BEFORE final rejection is (703) 872-9306. The fax phone number for responses to be filed AFTER final rejection is (703) 872-9307.


Questions which are NOT RELATED TO THE EXAMINATION ON THE MERITS, should be directed to **TC 1600 CUSTOMER SERVICE** at **(703) 308-0198**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Application/Control Number: 09/864,728

Page 8

Art Unit: 1641

April 26, 2003


Mary E. (Molly) Ceperley
Primary Examiner
Art Unit 1641